No. 14-378

IN THE

Supreme Court of the United States

STEPHEN DOMINICK MCFADDEN,
Petitioner,

v.

UNITED STATES OF AMERICA,
Respondent.

On a Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

BRIEF OF EXPERT FORENSIC SCIENTISTS AS AMICI CURIAE IN SUPPORT OF PETITIONER STEPHEN MCFADDEN

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INTEREST OF AMICI CURIAE[1]

Amici curiae are expert scientists within the fields of forensic chemistry, forensic toxicology, pharmaceutical design, and drug detection analysis who have conducted research at some of the world's leading medical schools, universities, and government laboratories. They include members of the American Academy of Forensic Sciences, American Chemical Society, Northeastern Association of Forensic Scientists, American Board of Criminalistics.

Amici have all provided expert testimony on numerous occasions and are experienced with issues associated with the Controlled Substance Analogue Enforcement Act ("CSAEA"). The question presented is specifically focused on the requisite intent for criminal prosecution under the CSAEA, however, prior to arriving at this question, an examination must be conducted in order to determine whether the substance in question is "substantially similar" to a controlled substance and thus, is found to be a controlled substance analogue. 21 U.S.C. §§ 802, 813.

Amici submit this brief on behalf of the defendant, with the intent to call the Court's attention to the statute's failure to define the term "substantially similar" and the problems that exist based on the absence of meaning within the scientific

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[1] No counsel for any party authored this brief in whole or in part, and no other person or entity other than amici or their counsel made a monetary contribution to its preparation and submission except for Edward J. Westbrook, who contributed monetarily to printing and production costs based on his affiliation with the Charleston School of Law. A consent letter on behalf of all the parties is on file with this Court.

community. Amici represented in this brief support the criminal prosecution of individuals who seek to manufacture or distribute illegal substances but have genuine concerns over the inconsistent, dissonant, and subjective application of methods used to determine whether an alleged substance is "substantially similar" as there is no reference material or method for this determination generally accepted within the field. As such, they have an important interest in not just the question presented to the court but the lack of meaningful minimum standards in order to do so. Amici include:

Joseph P. Bono, M.A., D-ABC is an independent forensic science consultant specializing in drug analysis with over 40 years of experience. He has worked at various levels of government, most notably, as a forensic scientist for the Drug Enforcement Administration and as the Laboratory Director for the United States Secret Service. He has served on numerous committees such as the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG), which recommends drug analysis and identification standards to laboratories worldwide; Chairman of the Virginia Forensic Sciences Board; and is the former President of the American Academy of Forensic Science. Mr. Bono is also a former adjunct professor in the Forensic and Investigative Sciences Program at Indiana University-Purdue University.

Anthony P. DeCaprio, Ph.D., DABT is an Associate Professor of Chemistry and Biochemistry and the Director of the Forensic and Analytical Toxicology Facility and Forensic Science Certificate Program for the International Forensic Research Institute at Florida International University. He is certified in General Toxicology by the American

Board of Toxicology and has extensive experience in chemistry and drug analysis, neurotoxicology/ neuropharmacology of drugs and chemicals, as well as biomarkers of drug and chemical exposure. He has published over 70 research papers in peer-reviewed journals and written several chapters for reference works in toxicology. Dr. DeCaprio has delivered more than 100 research papers and invited lectures; serves on the editorial board of two journals; and is a member of multiple professional organizations.

Francis Diamond is the Technical Leader in the Criminalistics Division of NMS labs and has 34 years of experience as a research scientist. His expertise includes techniques of separation and detection. He has developed analytical methods for the measurement of various drugs to include amphetamines, opiates, and benzodiazepines. Mr. Diamond has authored numerous papers in the field of analytical toxicology and participated in collaborative studies with instrument manufacturers and government agencies. He is also an Adjunct Professor at the Center for Forensic Science Research and Education at Arcadia University.

Paul L. Doering, M.S. is an Emeritus Distinguished Service Professor of Pharmacy practice at the University of Florida College of Pharmacy. He is also Co-director of the Drug Information and Pharmacy Resource Center. His research interests include drug information and interactions, and toxicology of drug products. Mr. Doering has been a consultant in legal matters for over 35 years. During this time, he has often consulted with the United States Drug Enforcement Administration (DEA) in both civil and criminal matters involving drug diversion by pharmacists and other health professionals.

Gregory B. Dudley, Ph.D. is an Associate Professor of Organic Chemistry and Associate Chair in the Department of Chemistry and Biochemistry at Florida State University. His expertise is in synthetic organic chemistry and his research focuses on organic reaction development and the chemical synthesis of natural products and drug-like compounds. Dr. Dudley's research efforts have resulted in over 80 written publications, over 100 invited seminar presentations, six patents, and two commercial products. He provides expert peer-review services for leading journals and funding agencies. Additionally, Dr. Dudley has been recognized by numerous awards and honors related to research, teaching and innovation.

Mark S. Erickson, Ph.D. is an Associate Professor of Chemistry at Hartwick College. His research interests include organic and organometallic conducting polymers and his research group is focused on the synthesis of molecules for use in conducting or semiconducting polymers. Dr. Erickson has been an independent chemistry consultant for 18 years, during which time he has provided expert testimony and analysis based on his expertise in Structural Analysis and Chemical Education. He has authored over 17 publications and is a member of multiple professional organizations to include the American Chemical Society.

Heather L. Harris, M.F.S., J.D., D-ABC is a certified independent forensic chemistry consultant and Professor of Forensic Chemistry at the Center for Forensic Science Research and Education at Arcadia University. Ms. Harris has worked as a forensic chemist at NMS Labs and in the Bexar County Criminal Investigations Laboratory in San Antonio, Texas where she performed drug and clandestine lab

analysis. Ms. Harris holds a Master of Forensic Science degree, is a licensed attorney, and has over twelve years of expertise in analytical techniques and subsequent legal interpretations of forensic scientific evidence within the areas of criminal and regulatory drug law and is certified as Diplomate in General Criminalistics and Drug Analysis by the American Board of Criminalistics. She actively participates in a number of professional organizations, most notably, she was a member of the Advisory Committee for the Evaluation of Controlled Substance Analogs (ACECSA), and served as Structure Evaluation Subcommittee Chair whose goal was to develop a protocol for the objective and consistent comparison between structures of alleged controlled substance analogs and scheduled drugs.

Lindsay E. Reinhold, M.F.S., F-ABC is a senior scientist in the pharmaceutical services industry and an independent Forensic Chemistry Expert with 14 years of experience in the field of Forensic Drug Analysis. She has a Master of Forensic Science degree and is certified as a Diplomate by the American Board of Criminalistics in Drug Analysis. Ms. Reinhold has worked as a Forensic Chemist at NMS Labs where she analyzed evidence to identify and confirm controlled substances using chemical microscopic and instrumental methods at a rate of approximately 200 cases per month. She also worked as a Criminalist in the New York City Police Department, Forensic Investigation Division where she was trained in the scientific and legal background of controlled substance analysis. Ms. Reinhold is an active member in a number of professional organizations, and most notably, she was the co-founder of the ACECSA.

Terry Stouch, Ph.D. has 25 years experience in drug discovery research in pharmaceutical and biotechnology specializing in drug design, molecular property prediction, structure, evaluation and modeling. He is President of Science for Solutions, LLC, a consulting firm specializing in molecular and computational sciences; Advisor to BioPharma Research Council, and Adjunct Professor in the Department of Chemistry and Biochemistry, Duquesne University. He is a Fellow of the American Academy for the Advancement of Science and the International Union of Pure and Applied Chemistry. He has participated in several federal hearings and as an expert in trials related to this matter and is a member of the Pistoia Alliance and also served on the ACECSA.

SUMMARY OF ARGUMENT

The purpose of this amicus brief is to highlight problems associated with the term "substantially similar" within the Controlled Substance Analogue Enforcement Act of 1986. 21 U.S.C. §§ 802, 813 (2013) ("CSAEA"). The issues are significant and relevant to this Court's analysis of the prosecutorial requirements under the statute.

The CSAEA provides that, to the extent a controlled substance analogue is intended for human consumption, it is to be treated as a schedule I controlled substance for purposes of any federal law. *Id.* The CSAEA was designed to combat the problem of persons who seek to avoid the reach of federal criminal drug laws by manufacturing or distributing substances that are not listed as controlled substances, but which are specifically designed to provide effects that are "substantially similar" to the effects of listed substances.

The primary challenge of an alleged analogue evaluation is that the statutory provision set out in 21 U.S.C. § 802(32)(A)[2] does not define "substantially similar." The classification of two chemical substances as "substantially similar" for the use in the legal system is concerning for two reasons.

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[2] For example, the CSAEA states that "the term 'controlled substance analogue' [includes] a substance . . . (i) the chemical structure of which is *substantially similar* to the chemical structure of a controlled substance in schedule I or II." *Id.* (emphasis added). However, the statute is devoid of a definition for "substantially similar." *See id.*

First, the phrase "substantially similar" has no quantifiable meaning and, thus, no objective criteria for its measurement exist. There simply is no established and agreed upon rubric in the scientific community to measure structural similarity. Additionally, neither the field of forensic chemistry, nor any major academic, government, or technical forensic science entity has developed a standard definition for "substantially similar" or a standard method for the evaluation of alleged analogs.

Second, when attempting to compare either chemical structures or the effects of the two substances, scientists do not agree on what should be compared, nor the weight each comparison should be given. In other words, similarity depends on what is being compared, whether it is core structure, functional group, or some other factor. Further, even if scientists were to agree on what to compare within the chemical structure of two molecules when comparing the structural similarity, the CSAEA fails to provide a defined threshold where ordinary similarity ends and substantial similarity begins.

ARGUMENT

The definition of "controlled substance analogue" has two requirements. For a substance to satisfy the definition of "controlled substance analogue," the substance at issue must (1) have a chemical structure that is "substantially similar to the chemical structure of a controlled substance in schedule I or II" (structure prong), and (2) it must have an effect that is "substantially similar" to a controlled substance in schedule I or II (effect prong). 21 U.S.C. § 802(32)(A) (2013).[3] This provision sounds simple on its face, but it is a complex and unsettled area in forensic chemistry. The phrase "substantially similar" has no quantifiable meaning and, thus, no objective criteria for its measurement exist. This statutory language demands a substance by substance evaluation and interpretation, often based on little more than subjective feelings about the appearance of two-dimensional diagrams. *See United States v. Brown*, 415 F. 3d. 1257, 1261-63 (11th Cir. 2005). This approach discourages scientific discussion and

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[3] The second requirement above may be satisfied by showing the substance at issue produces *either* a substantially similar effect as a controlled substance, *or* that "a particular person . . . represents or intends" the substance to have a substantially similar effect as a controlled substance. *Id.* (emphasis added). The conjunctive reading of these two prongs has been accepted by the "vast majority of federal courts." *United States v. Turcotte*, 405 U.S. 515, 522 (7th Cir. 2005). In *United States v. McFadden*, "both parties advocated for a conjunctive reading of the statute, [and] the court assumed, for purposes of this case, that it is the correct one." *United States v. McFadden*, 15 F. Supp. 3d 668, 672 n.2 (W.D. Va. 2013), *aff'd*, 735 F.3d 432 (4th Cir. 2014).

currently results in disparate opinions by chemists, thus showcasing the lack of consensus in the field.

Therefore, the difficulty arising from the definition of "controlled substance analogue" is that "substantially similar" is not itself defined, leaving courts, attorneys, and experts in disagreement as to its meaning and the sufficiency of evidence required to prove "substantial similarity." A consequence is that "[a] substance's legal status as a controlled substance analogue is not a fact that a defendant can know conclusively *ex ante*; it is a fact that the jury must find at trial." *United States v. Turcotte*, 405 F.3d 515, 526-27 (7th Cir. 2005).

Generally, to decide whether a substance is "substantially similar" to a scheduled controlled substance, juries must resolve the conflicting claims of expert witnesses on complex matters of scientific methodology, chemistry, and biology. *See, e.g.*, *United States v. Brown*, 415 F.3d 1257, 1261-63 (11th Cir. 2005); *United States v. Forbes*, 806 F. Supp. 232, 237 (D. Colo. 1992) (noting defendant was prosecuted despite the fact that the "government's own chemists cannot agree" on whether the substance at issue met the "substantial similarity" test, perhaps in part because the "scientific community cannot even agree on a methodology to use to determine structure similarity").

The resolution of this issue by juries has proved problematic because the term "substantially similar" has no scientific meaning, there is no definition to help determine when two similar structures become "substantially" similar, and there is a lack of scientific consensus as to how to compare *structural* similarity or *effect* similarity.

I. The Term "Substantially Similar" Has No Scientific Meaning.

There is no scientific consensus for determining when two chemicals are "substantially similar." The standard is a legal construct with no scientific definition and there is no established methodology accepted by the scientific community that can measure this term.

One of the principles underlying the scientific method is that it provides a systematic approach to knowledge. By creating hypotheses that are capable of being tested, the information collected from such tests adds reliability to the truth or falsity of the hypotheses. Similarly, the ability of a test to be repeated, producing consistent results, adds to the reliability of the hypotheses. In short, the uniformity of the test and the results allows for the hypotheses to be confirmed or denied, thereby adding to a scientific knowledge base that can be relied upon.

We are at the hypothesis and observation stage of the scientific method with respect to comparing analogues. There are no tests, no experiments, or established methodologies. There are no peer-reviewed articles or textbooks directly addressing the meaning of "substantially similar" that a scientist can look to for help. Because of this, scientists are left to form opinions based on their own individual methods and interpretations, but these are not and should not be considered scientific conclusions.

The term "substantially similar" is simply not used to quantitatively compare the structures of two molecules, nor is the parameter defined in instructive articles or textbooks that are publically available through externally peer-reviewed scientific literature. There is no consensus or agreed upon scientific

methodology to determine whether one substance is "substantially similar" in structure to another. There simply is no standard methodology for the qualitative and/or quantitative measure of "substantial similarity" between chemical structures.

This lack of consensus is not simply the opinion of the amici who are submitting this brief to the Court, but has been documented in open court by testimony of government experts who were ultimately called to conclude that two compounds were substantially similar.

In *United States v. Brown*, one of the government's expert witnesses, Dr. Richard Irwin,[4] testified that there is no universal agreement on what constitutes a "substantially similar chemical structure," and that ***"it's pretty much a gut level thing."*** Transcript of Trial[5] at 42, *United States v. Brown*, 279 F. Supp. 2d 1238 (S.D. Ala. 2003) (No. CR.A. 02-00185), *aff'd*, 415 F.3d 1257 (11th Cir. 2005) (emphasis added).

The cross examination of Dr. Thomas DiBerardino,[6] a DEA chemist and expert for the government in *United States v. McFadden*, concisely states the issue:

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[4] Dr. Richard D. Irwin, National Institute of Environmental Health Sciences.

[5] The Transcript of Trial is not consecutively paginated. This document is Volume II of the Transcript of Trial, document # 264.

[6] Dr. Thomas DiBerardino, Chemist, DEA, Office of Diversion Control, Drug & Chemical Evaluation Section.

> Q: Is there a scientifically commonly understood definition to substantially similar?
>
> A: I don't think so, no.

C.A. J.A.[7] at 474, *United States v. McFadden*, 15 F. Supp. 3d 668 (W.D. Va. 2013) (No. 3:12-CR-00009), *aff'd*, 753 F.3d 432 (4th Cir. 2014).

It appears that the only consensus among the scientific community is that there is no consensus when it comes to interpreting the term "substantially similar."

Standards are not a choice of the person claiming to be an "expert witness." Nor can standards in forensic science be formulated individually to fit the argument of either the government or the defense. Standards in forensic science cannot be formulated individually. Expert witnesses are entitled to their own opinions which must be substantiated by supporting reliable data, however, expert witnesses are not entitled to the privilege of creating their own facts. Claiming that "the chemical structure [of a substance] is substantially similar to the chemical structure of a controlled substance in schedule I or II" without a detailed explanation and reference to an acceptable standard or definition, in effect elevates the expert into the role of a law maker rather than as

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[7] Because the trial transcript is not consecutively paginated, this brief will refer to the transcript by reference to the page numbers in the Joint Appendix filed with the court of appeals and available on Pacer at Docket No. 19.

an expert expressing an opinion based on a scientific standard.

II. Without Defined Standards, Scientists Must Decide On A Case-by-Case Basis What To Compare Within Each Substance Resulting In Subjective Opinions That Vary Widely.

Because neither the field of forensic chemistry, nor any major academic, government or technical forensic science entity has developed or promoted a standard definition for "substantially similar," or a standard method for evaluation of alleged analogues, scientists must subjectively decide what approach to use when evaluating the similarity of compounds. Numerous problems arise because of this lack of a scientific standard. As it relates to the similarity in chemical structure, scientists do not have any guidance as to what they are comparing within the chemical structure of the two molecules. Further, even if scientists agreed as to what was most important about the chemical structure, no definition exists to guide the opinion as to when something similar becomes "substantially similar." Finally, when comparing the effects of two substances, scientists are left with undefined parameters in deciding what is most significant.

A. Similarity Depends On What Is Compared Within The Chemical Structure Resulting In Divergent Subjective Opinions.

Scientists do not agree which components of a substance's structure should be compared to assess similarity and how much weight should be given to each component. There are simply too many perspectives to take in comparing structures. Each

method will draw its own conclusion, sometimes with different conclusions even using the same method.

Even someone without a Ph.D. in Organic Chemistry can understand that the term "structure" when applied to a chemical substance can refer to many things. Regardless of whether a non-chemist understands the science behind each of the examples below, the mere variety in the methods is evidence that they are necessarily going to lead to subjective choices which then lead to inconsistent conclusions. In other words, the following examples simply demonstrate that when chemists talk about chemical structure, they can be referring to many different aspects of how the chemical is put together.

For example, one method may place particular importance on whether the two molecules share the same functional groups,[8] whether they have the same core structure, and examine the prevalence and location of reactivity-modifying double bonds. This one method shows the variety of factors that can be compared: core structures include the rings and chains that compose the base structure of the molecules; functional groups include the additional structural features, such as alcohols, amines and ketones, that determine chemical reactivity and metabolism; and finally, the presence and location of

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[8] "Organic compounds are thought of as consisting of a relatively unreactive backbone, for example a chain of hybridized carbon atoms, and one or several functional groups. The functional group is an atom, or a group of atoms that has similar chemical properties whenever it occurs in different compounds. It defines the characteristic physical and chemical properties of families of organic compounds." INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY, COMPENDIUM OF CHEMICAL TERMINOLOGY GOLD BOOK 605 (Ver. 2.3.3 2014).

double bonds, particularly conjugated double bonds or double bonds proximal to functional groups, impact both the reactivity of a molecule as well as its three-dimensional structure.

Another method that might be used broadly finds similarities between two structures by picking shared fragments such as an indole moiety[9], even though the indole moiety is a common fragment and is shared by thousands of other compounds. The same could be said about considering the indazole, phenyl, and naphthyl moieties in a comparison exercise. So, in fact, the structures are not directly compared, but instead, similarity depends on commonly held structural fragments.

Other methods may consider shared carbon skeletons or structural classes. These examples simply demonstrate that the term "structure" when applied to a chemical substance can refer to many things.

One of the primary problems that arises from these subjective choices is that it is logically impossible from any perspective to argue that two chemicals are substantially similar, and at the same time acknowledge that they possess differences in chemical formulations, synthesis protocols, molecular weights, electronegativity, bond lengths, and bond angles. And when these variances in chemical formulation result in divergences in chemical

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[9] "In physical organic chemistry moiety is generally used to signify part of a molecule, e.g. in an ester R^1 COOR^2 the alcohol moiety is R^2O. The term should not be used for a small fragment of a molecule." INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY, COMPENDIUM OF CHEMICAL TERMINOLOGY GOLD BOOK 946 (Ver. 2.3.3 2014).

properties and resulting analytical data, the "substantially similar" and "chemical structure" arguments become even more illogical and move even further away from scientifically reliable conclusions.

1. The Common Use Of Two-Dimensional Line And Letter Representations Are Misleading And Insufficient.

Dr. DiBerardino testified in *McFadden* with the aid of two-dimensional diagrams, exhibits commonly misused by government experts in drug analogue cases. C.A. J.A. at 440 ("I'm going to show you a number of exhibits and ask if you would identify them."); *see* Gov't exhibits 75-83 (all two-dimensional diagrams including some that superimpose the alleged analogue structure and the controlled substance structure for the jury's comparison.) *Id.* at 440-64.

Two-dimensional diagrams are often used to simplify the complexities of the chemical structures being compared, but result in an oversimplification. In fact, when Dr. DiBerardino testified at trial, he explained on direct examination that he even left out information from the diagram because it might be too confusing:

> It's only because when you start adding all these carbon groups and whatnot, *it gets very, very busy*. . . .
>
> When we talk about structure, the analysis is based on those [carbon and hydrogen atoms] being there, but we don't have to

> look at them again because *it just gets too noisy*. It would just be too hard to decipher through all that.

Id. at 444. (emphasis added)

Two-dimensional structures using stick and letter drawings of molecules do not even begin to represent to the untrained observer the reality of "chemical structures," which exist dynamically in three-dimensional space. Any comparison of chemical structures which relies upon an evaluation of two dimensional representations for the purpose of justifying or arguing structural similarity is problematic at best, and at worst will unintentionally mislead a non-scientist into believing an "expert's" assertion on the mere basis that it is asserted by an "expert."

Two-dimensional stick and letter diagrams are misleading. Two-dimensional cylindrical bond "stick and ball" diagrams, while being a bit better in their depiction of three-dimensionality, still fall short of accurately depicting the reality of chemical structure to determine structural similarity. Three-dimensional cylindrical molecular structures in combination with three-dimensional "cluster" molecules are much better representations for scientists (and especially for non-scientists) to determine whether the requirements of reliable and relevant evidence exist. Only when the nature of the structures is understood can the discussion of molecular structure and the comparisons move forward.

An additional difficulty with stick and letter drawings is they do not show molecular structural

dynamics, nor do they include all of the atoms which comprise the individual "chemicals" which are being reported. It is easy to understand how a non-chemist could look at these drawings without understanding what they represent and agree with anything an expert chemist might assert about them. The interpretation of scientific notation, represented in these stick and letter drawings, by non-scientists, even by those trained in the law, is problematic without a basic understanding of what this notation means.

Two-dimensional stick and letter drawings are essentially "codes" that trained chemists can interpret to gain an understanding of the true three-dimensional shape and dynamics. However, this "code" takes years of study to learn and understand. It is even more problematic for a scientist to use chemical notations in a non-scientific forum like a courtroom without direct explanations of exactly what those notations mean.

Any reporting of or testimony related to structural similarity between two different molecules based on a visual inspection of two-dimensional drawings does not meet the requirements for scientific reliability in the laboratory. In fact, Dr. DiBerardino admitted on direct examination during trial that he was simply "drawing pictures" and "staring at a computer" and was "not in a lab." *Id.* at 440. In the absence of corroborating data and more information, there are few if any credible forensic chemists who would base any conclusion of similarity solely on two-dimensional diagrams. Trained chemists, upon reviewing a two-dimensional molecular drawing, automatically "translate" the

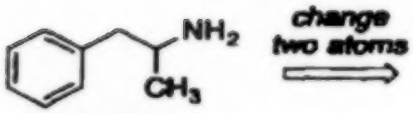
code to consider the proper three-dimensional and dynamic structure. In fact, the first question a credible forensic chemist asks in any kind of a forensic analysis where a comparison is the basis for a conclusion is: "Are there differences in what is being observed in the comparison?" And if differences do exist, they will usually result in a qualified conclusion that the entities being compared are different.

2. The Approach Used By The Government In *McFadden* To Determine "Substantial Similarity" Is Overly Broad And Leads To Absurd Results.

The government's argument, in *McFadden*, for assessing the similarity between chemical structures is overly broad and can lead to absurd results. The identified "core structure," phenethylamine, forms a small part of the molecule and defines a structural category so large that it results in being over inclusive. The government's argument – that changes occurring on the periphery are not "substantial" — is invalid and produces absurd results. The comparisons below illustrate the problems that could result from the government's argument. Additionally, these comparisons illustrate how two-dimensional diagrams can be overly simplistic and unintentionally mislead a non-scientist observer about the reality of a substance's chemical structure.

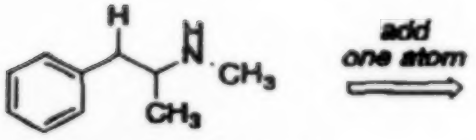
Functional groups matter

(GB Dudley, PhD)



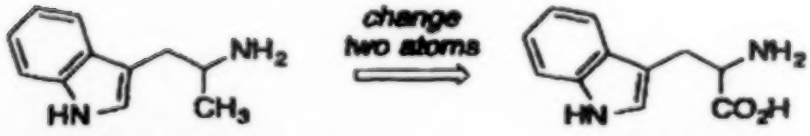
amphetamine
(drug of abuse)

phenylalanine
(essential amino acid)



methamphetamine ("meth")
(drug of abuse)

pseudoephedrine (Sudafed)
(non-prescription decongestant)



alpha-methyltryptamine (AMT)
(drug of abuse)

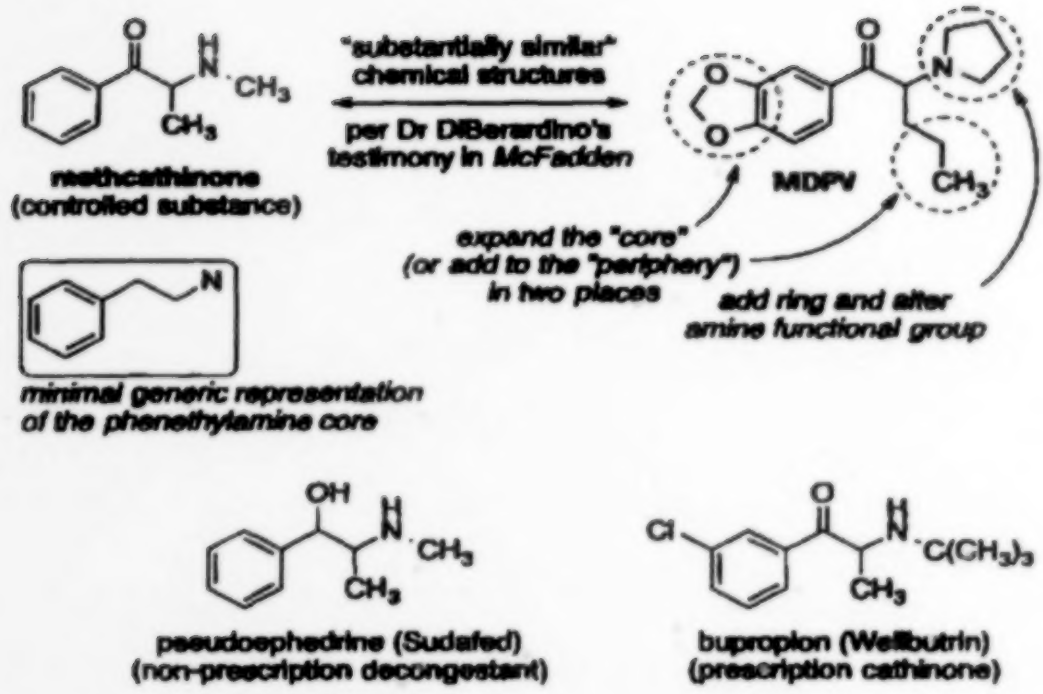
tryptophan
(essential amino acid)

Applying the government's "core structure with peripheral change" methodology along with two-dimensional representations, the essential dietary amino acids phenylalanine (top) and tryptophan (bottom) could be considered structural analogues of the controlled substances amphetamine and alpha-methyltryptamine (AMT), respectively. The structural differences in each case can be (simplistically) described as changing two atoms on the periphery. The fallacy of this analysis is that it ignores the importance of functional groups, but the significance of this change may not be obvious to non-chemists. Pseudoephedrine (middle) only has one

extra atom compared to methamphetamine. Pseudoephedrine is controlled because it can be converted chemically into methamphetamine, not because it is "substantially similar" to methamphetamine, although they are both phenethylamines that differ only by a single atom on the periphery. Clearly the government's methodology in *McFadden* cannot be applied consistently.

Whatever methodology ultimately emerges for determining what is or is not "substantially similar" will have to recognize the importance of functional groups in comparing chemical structures.

The "core" and "periphery" of chemical structures are often themselves subjective constructs of the human mind that reflect individual biases toward specific structural features. The same compound may be given different names (e.g., "cathinone" or "beta-keto amphetamine") by different people who prioritize differently the defining structural features. In cases where there are true "core" (interior) and "periphery" (exterior) structural features, the peripheral features generally have a greater impact on chemical properties because of their greater exposure to neighboring molecular structures.



In *McFadden*, to determine that Methylenedioxypyrovalerone ("MDPV") is "substantially similar" in chemical structure to methcathinone based on their shared phenethylamine core, one would have to dismiss several expansions of the "core" structure (or additions to the "periphery," depending on one's individual biases) as well as an alteration to the amine functional group, while also disregarding structures like those of legal substance like pseudoephedrine and bupropion, which might reasonably be deemed more similar to methcathinone than is MDPV.

The lack of boundary conditions on what can be deemed "substantially similar" allows for arbitrary, inconsistent, and potentially absurd interpretations. Most egregiously, features deemed "important" in one case might later be deemed "unimportant" in a different case.

Notwithstanding these potentially absurd results, a "core structure with peripheral changes" approach still does not clarify the legal status of an unknown chemical structure. If the CSAEA stated that an analogue was a substance with a core structure similar to that of a Schedule I or II controlled substance with only peripheral changes, disagreements would still persist in the scientific community. One chemist might see the phenethylamine core structure present in Methcathinone and MDPV and consider them analogues. However, another chemist might consider the core structure of MDPV to include all 3 ring structures meaning it would not meet the core structure criterion. In other words, even if scientists agreed at a general level that the appropriate way to measure "substantial similarity" is by comparing the degree of alteration from a common core, there would still be disagreement about how to define a chemical's "core."

Regardless of how a scientist breaks down the analysis of chemical structure, without guidelines, rules, or acceptance criteria, there will always be disagreements in the scientific community. If the scientific community cannot agree, how could a lay-person, such as a juror, be expected to know whether the substance in question was a controlled substance or not?

B. There Are No Quantifiable, Objective Criteria For Determining When Similarities Between Substances Become "Substantial."

Even if scientists agreed on what they were comparing within the chemical structure, the CSAEA language fails to provide a defined threshold where

ordinary similarity ends and substantial similarity begins. When trying to determine whether one chemical structure is "substantially similar" to another, a scientist must ask, "What threshold is necessary to say the structures are *substantially* similar?" Are the two structures substantially similar if 51% of the structures are the same? 75%? 95%? It is left to a scientist to establish the answers to these questions for herself as there are no widely accepted answers to these questions. Scientists have no guidance based on actual science to answer these questions.

Because there are simply no quantifiable, objective criteria for determining when similarities between substances become "substantial," courts are left to make such a determination on a "case-by-case," or "substance-by-substance" basis. In the absence of a universally accepted objective and quantitative measure of similarity, the phrase "substantially similar in structure" gives no guidance to confidently, or reliably conclude whether any change in structure qualifies as significant or not, resulting in a subjective determination heavily influenced by each individual user's perspective. "Substantially Similar" lacks a defined measurand, without which, the magnitude of similarity cannot be quantified.

The CSAEA fails to define the magnitude of similarity required before "substantially" similar relationships are determined. Known error rates, measurands, thresholds, and calibration standards cannot be determined, resulting in similarity comparisons that are susceptible to user and methodology-dependent conclusions leading to divergent interpretations and bias between analysts.

Consequently, the analysis is subject to designing the test in order to have the result desired. What we see and report as scientists should not be dependent upon what we are looking for.

C. Scientists Cannot Accurately Determine "Substantial Similarity" Of The *Effects* On The Central Nervous System Of Different Substances Because There Are No Defined Criteria In The CSAEA.

The second criterion for inclusion of a compound as a controlled substance analogue is defined by 21 U.S.C. §802(32)(A) as a substance: "(ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in Schedule I or II." The term "substantially similar" as to effect is no more defined than the term "substantially similar" when applied to chemical structure.

Pharmacological effects in humans are by their nature nuanced, graded, and variable. A "stimulatory" effect produced by two drugs that, on the surface, appears "similar," may in fact be due to radically different pharmacological mechanisms. The phrases "pharmacological activity" and "pharmacological effect" are ambiguous and could refer to one of an almost unlimited variety of pharmacological properties. Examples of such properties include binding affinity of drugs to membrane and cytoplasmic receptors, enzymes, transporter molecules, DNA, RNA, or other molecular targets in addition to specific drug effects on liver,

renal, central nervous system, lung, or any of a myriad of specialized cells.

Such properties can also refer to functional effects on cognition, physiological parameters such as blood pressure and heart rate, sexual function, appetite, behavior, memory, or locomotion. Consequently, two drugs may cause similar effects on one pharmacological endpoint (like blood pressure) but totally different effects on another (like motor activity), making comparative evaluation of the two drugs under the simplified criteria of the CSAEA virtually impossible.

The psychotropic effects of drugs of abuse almost always involve binding and activation (or inhibition) of specific receptors for neurotransmitter or other neuroactive molecules in the central nervous system. In order to assess the ability of prototypical drugs to produce these effects, initial studies often employ measurement of binding affinity with isolated receptors or cell membranes containing the receptors. These experiments are performed *in vitro*, i.e., in an artificial "test tube" system outside of a whole animal or human being. There are significant problems with attempting to extrapolate *in vitro* binding or neurotransmitter release data determined for one drug to another untested, but chemically related compound. This is because small structural differences in drug molecules can lead to large changes in transporter or receptor binding affinity, thus potentially leading to major pharmacological differences. Consequently, the appropriate use of such assays is only to indicate which compounds may be considered for further testing.

Since it is impossible to predict with confidence how *in vitro* data will translate into pharmacological

effects in living systems, the objective and accurate prediction of central nervous system activity of drugs in humans based on *in vitro* data alone is unreliable. Thus, at the very least, a sound and reliable analogue drug scheduling approach should involve assessment of stimulant, depressant, or hallucinogenic effects in animal models in addition to corroboration from human data.

The CSAEA does, after all, specify that these effects be demonstrated "*on the central nervous system,*" a requirement that cannot be achieved by *in vitro* testing or structure-activity considerations alone. *Id.* (emphasis added).

Animal models assess behavioral pharmacology endpoints such as locomotor activity, catalepsy, drug discrimination and self-administration responses, in addition to physiological measurements such as body temperature. While offering additional data on the potential central nervous system activity of candidate drugs, these models all suffer from shortcomings when used to predict similar (i.e., qualitative and quantitative) effects in humans, and therefore are best considered suggestive but not selective or definitive tools. Consequently, they are typically employed in pharmaceutical development as screening assays to either identify appropriate drug leads for further testing or to eliminate drugs that may exhibit undesirable activity at an early stage of development.

In contrast, the use of such behavioral and physiologic assays for definitive comparisons and predictions of relative drug activities in humans is problematic. Such a goal would require rigorous attention to negative and positive controls, variance in within- and between-test results, and an ability to

identify what specific effect the animal is responding to (i.e., a typical drug will produce multiple effects, any of which could lead to the same behavioral response). It can be reasonably argued that these tests are not highly predictive, as there are multiple examples of false positive results (i.e., drugs that substitute for the training drug but do not produce similar effects in humans). The bottom line is that no one really knows what the animal is actually perceiving or responding to, therefore the test is best used only for preliminary evaluation of human psychoactive potential.

In summary, asking scientists to accurately compare two substances to determine "substantial similarity" as to the effects of those substances sets a standard that cannot be satisfied in the absence of actual human data. *In vitro* and animal models alone are insufficient to predict with a high level of confidence the possible central nervous system stimulant, depressant, or hallucinogenic effects of novel compounds in humans. This is why drugs developed for the market are ultimately tested in human trials.

CONCLUSION

For the foregoing reasons, the judgment of the court of appeals should be reversed.

Respectfully submitted,

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